

REMARKS

Claims 1, 4, 7, 8 and 20-23 are pending. Claims 2 and 3 are withdrawn from consideration. Claims 5-6 and 9-19 are canceled. Claims 1, 4, 8, 20 and 23 are amended. No new matter is added.

Claim 1 has been amended to state a method of screening for a human individual's predisposition to atopy, the method comprising analyzing said individual for presence of at least one TIM-1 polymorphism by contacting a biological sample comprising DNA or mRNA with probes that specifically bind under stringent conditions to nucleic acid sequences of a TIM-1 gene, where the presence of the polymorphism is indicative of an individual's predisposition to develop atopy. Support for the term "screening" is found in the specification on, e.g., page 53, paragraph 194. Support for the term "atopy" is found in the specification on, e.g., page 1, paragraph 01. Support for the term "DNA or mRNA" is found in the specification on, e.g., page 13, paragraph 51.

Claim 4 has been amended to replace the term "nucleic acids" with "DNA or mRNA".

Claim 8 has been rewritten in independent form; stating a method of screening for human individual's predisposition to atopy by detecting the presence of INS157 polymorphism in TIM-1 and analyzing that individual for HAV seropositivity. Support for this amendment is found in Claim 1. Support for screening for presence of INS157 polymorphism in TIM-1 is found in the specification on, e.g., page 13, paragraph 51.

Claim 20 has been amended to state a method of screening for a human individual's predisposition to atopy, by detecting the presence of INS157 polymorphism in TIM-1, by contacting DNA or mRNA from the individual with a probe that specifically binds to the INS157 sequence.

Claim 23 has been amended to state a method of screening for a human individual's predisposition to atopy by analyzing the individual's biological sample for presence of at least one polymorphism in exon 3 of TIM-1 gene, the method comprising detection of at least one polymorphism in exon 3 of TIM-1 gene by using probes that specifically bind to polymorphisms in exon 3 of the gene. Support for the term "probes" is found in the specification on, e.g., page 15, paragraph 59.

As no new matter has been added by way of this amendment, entry thereof by the Examiner is respectfully requested.

In view of the following remarks, the Examiner is requested to allow claims 1, 4, 7-8 and 20-23, the only claims pending and under examination in this application.

REJECTIONS UNDER §112, ¶1

Claims 23 has been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Office Action states that the specification does not teach "probes specific for any polymorphism in exon 3 of the TIM-1 gene".

Without any intention to acquiesce to the correctness of this rejection and solely to expedite prosecution, claim 23 is amended to state a method of screening for a human individual's predisposition to atopy by analyzing the individual for presence of at least one TIM-1 polymorphism in exon 3 by using probes that specifically bind to polymorphisms in exon 3 of TIM-1. The Applicants submit that this aspect of the rejection has been addressed.

Claims 1, 4, 7-8 and 20-23 have been rejected under 35 U.S.C. 112, first paragraph. Specifically, the Office Action asserts that while the specification is enabling for a method for determining a Caucasian's predisposition to atopy protection by detecting the presence of the homozygous polymorphism of 157insMTTVP of TIM-1 in a hepatitis virus A positive Caucasian individual, wherein the presence of the MTTVP insertion is indicative of a Caucasian's predisposition to be protected against atopy, it is not enabling for a method for diagnosing an individual's predisposition to any atopic immunological disorder by analyzing for the presence of any TIM-1 polymorphism.

Independent Claim 1 as presently amended recites a method of screening for a human individual's predisposition to atopy, the method including, analyzing the individual for the presence of at least one TIM-1 polymorphism by contacting a biological sample comprising DNA or mRNA from the individual with probes that specifically bind under stringent conditions to nucleic acid sequences of a TIM-1 allele, where the presence of the polymorphism is indicative of an individual's predisposition to develop atopy. Claim 8 specifically refers to detection of the INS57 polymorphism and HAV seropositivity. Claim 20 specifically refers to detection of the INS157 polymorphism, and Claim 23 to polymorphisms in exon 3.

The law regarding enablement of inventions is clear: “[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.”¹

To comply with 35 U.S.C. § 112, first paragraph, a specification need only enable a skilled artisan to make and use the claimed invention without undue experimentation. Accordingly, a specification complies with the statute even if a reasonable amount of experimentation is required, as long as the experimentation is not “undue”. As reviewed in the Office Action, one way to determine if undue experimentation is required is to analyze the subject specification in light of the *Wands* factors:² (1) the breadth of the claims, (2) the nature of the invention, (3) the state of the prior art, (4) the predictability or unpredictability of the art, (5) the quantity of experimentation necessary, (6) the relative skill of those in the art, (7) the amount of direction or guidance presented, and (8) the presence or absence of working examples. However, all of the factors need not be reviewed when determining whether a disclosure is enabling.³

Applicants respectfully submit that, when evaluated in view of the relevant *Wands* factors, the specification clearly enables one of skill in the art to practice the subject invention without undue experimentation. In other words, Claims 1, 4, 7-8 and 20-23 recite subject matter that is adequately described in the specification in such a way as to teach a skilled artisan how to make and use the claimed invention without having to practice undue experimentation. The relevant enablement factors cited in the Office Action are discussed in detail below.

The nature of the invention and the breadth of the claims

The claims as amended are drawn to a method of screening for a human individual’s predisposition to atopy by analyzing the presence of at least one TIM-1 polymorphism where the presence of the polymorphism is indicative of individual’s predisposition to develop atopy. The claims are further drawn to a method of contacting a biological sample, with a probe that specifically binds to the nucleic acid sequence of MTTTVP or with probes that specifically bind

¹ *United States v. Telectronics, Inc.*, 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), cert. denied, 490 U.S. 1046 (1989). See also *Genentech, Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (Fed. Cir. 1997), cert. denied, 522 U.S. 963 (1997); *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

² *In re Wands* 8 USPQ2d 1400 (Fed. Cir. 1988)

³ See *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991)

to polymorphisms in exon 3 of TIM-1 gene and which may further comprising a step of analyzing an individual for presence of Hepatitis A virus seropositivity.

The Office Action states that the nature of the invention requires knowledge of a correlation between detection of the presence of a TIM-1 polymorphism and predisposition to develop an atopic immunological disorder. The Applicants submit that such a correlation is provided in the specification. A description of common polymorphisms in TIM-1 and the linkage of TIM-1 locus to development of atopy can be found in the specification on e.g., Page 8, paragraph 37-43; page 13, paragraph 51; page 46, paragraph 169-175 and page 53, paragraph 192-200.

The Office Action indicates that the specification does not teach an association with *any* atopic disorder. Applicants respectfully submit that atopy is a distinct medical condition, and it is shown in the instant specification that information regarding an individual's predisposition to atopy is obtained from analysis of polymorphisms in TIM-1.

Atopic immunological disorder or atopy is defined as an allergic hypersensitivity affecting parts of the body not in direct contact with the allergen. It includes eczema (atopic dermatitis), allergic conjunctivitis, allergic rhinitis and asthma. Atopy is a well characterised medical condition with underlying immune dysfunction which manifests in specific clinical phenomenon. The art refers to this condition in multiple references provided herein.

The applicants further submit that numerous publications have corroborated the correlation between detection of the presence of a TIM-1 polymorphism and predisposition to atopy. Sizing et al. in J. Immunol. 2007 Feb 15; 178(4):2249-61 describe using monoclonal antibodies against TIM-1 to show that TIM-1 influences the extent of lung inflammation. Graves et al. in J Allergy Clin Immunol. 2005 Sep; 116(3):650-6 report a 15-bp insertion/deletion in exon4 of TIM1 being significantly related to atopy.

The amended claims encompass screening for a human individual's predisposition to atopy by analyzing the individual for presence of polymorphisms in TIM-1 gene, where the presence of the polymorphism is indicative of the individual's predisposition to develop atopy. The claims do not encompass correlating the presence of a polymorphism to the development of atopy but rather the claims encompass presence of a polymorphism being indicative of the individual's predisposition to develop atopy. For example claim 20 recites detecting a common TIM-1 polymorphism, 157insMTTTVP, and associating its presence to the individual's predisposition to develop atopic disorder. Applicants are not claiming that every polymorphism

in TIM-1 is related to atopy. The applicants are limiting their claims to method of detecting polymorphisms in TIM-1, which information is useful to an individual wishing to evaluate their predisposition to atopy, and which information may be further evaluated in the context of HAV-1 seropositivity.

Guidance in the specification and working examples

The Office Action states that although determination of alleles is routine in the art, predictably correlating an allele to any type of atopic immunological disorder in any human individual is unpredictable and the specification does not predictably correlate each of these polymorphisms with any type of atopic immunological disorder in any human individual. Applicants respectfully disagree.

Applicants respectfully submit that the claims do not recite that every polymorphism in TIM-1 is related to an atopic disorder. The claims are limited to detecting polymorphisms in TIM-1 gene, which information is useful to an individual wishing to evaluate their predisposition to atopy, and which information may be further evaluated in the context of HAV-1 seropositivity.

Moreover, MPEP 2138.05 states that reduction to practice may be an actual reduction or a constructive reduction to practice. The instant specification shows, in multiple experimental examples, unambiguous evidence that the TIM-1 gene is associated with atopy. The constructive reduction to practice constituted by the present application thus provides both a rationale for the selection of the TIM-1 gene as a screening tool for atopic disorders and the means to effect such screening using TIM-1 alleles in individuals.

Since the instant specification provides: atopic conditions of interest to the claimed method, a detailed description of the TIM gene family including its chromosomal location and sequence content, molecular characteristics of the TIM gene products including sequence motifs and structural features, numerous referenced publications linking the TIM gene family to multiple atopic disorders, description of the important role of the TIM-1 gene in immunological responses, methods of isolating TIM genes from tissue samples, techniques for genotyping TIM alleles for the purpose of diagnosis, and typical methods of preparing and detecting probes, the specification provides everything that is needed such that the ordinarily skilled artisan can identify polymorphic allelic variants of TIM-1 associated with atopic conditions and use such polymorphisms for diagnostic purposes by employing straightforward techniques known to the art. Accordingly, the specification amply supports a constructive reduction to practice for any TIM-1 allele by the present application.

The Office Action asserts that although table 1 of the specification demonstrates that HAV positive subjects with the 157insMTTVP TIM-1 allele are associated with protection against atopy tables S3 and S4 demonstrate that 157insMTTVP is predictably correlative for only the Caucasian population that is HAV positive and homozygous for the allele and that neither the HAV negative or HAV positive population of Asian subjects is statistically relevant to diagnose a predisposition to any immunological disorder or atopy and table S3 demonstrates that the only statistically relevant data in the Caucasian subjects is for Caucasian subjects with HAV that are homozygous for 157insMTTVP allele. The specification asserts that the African American sample size was too small to present separately.

Applicants respectfully submit that this is incorrect. In both tables, consisting of subgroup analyses for Caucasian and Asian populations, the "157insMTTVP 1,2 vs 0 alleles" column reports a significant P value for HAV+ individuals, P=0.024 (odds = 0.105-0.870) and P=0.036 (odds=0.070-0.897), respectively. As such, the 157insMTTVP allele is predictably correlative for the group including seropositive heterozygous and homozygous individuals in both Caucasian and Asian populations. It is unclear why the Office Action states that this is not "statistically relevant" data.

Further, the lack of presentation of a subgroup analysis of African American individuals is due solely to the small n value of the group (specification, paragraph 202). Since the analysis according to Table 1 was performed using a Cochran-Mantel-Haenszel chi-square test with racial stratification (specification, paragraph 199), the statistical conclusion therein is valid for all included ethnicities.

The Examiner states that the specification does not teach the association of any polymorphism, other than 157insMTTVP allele, in TIM-1 gene with the risk of developing any type of atopic immunological disorder. The Applicants disagree with this statement. Numerous polymorphisms in TIM-1 gene and the linkage of TIM-1 gene to atopy are described in the specification on e.g. page 8, paragraph 37-38.

The Office Action states that the specification envisions hypothetical situations where any polymorphism in TIM-1 could determine the presence of an atopic immunological disorder. Applicants respectfully disagree. The specification teaches the use of a polymorphism in TIM-1 to determine a statistical likelihood (i.e. predisposition) of vulnerability to an atopic immunological disorder, not the presence or absence thereof. It is nowhere recited or implied in

the instant Application that every polymorphism of TIM-1 will carry predictive association with an atopic disease. The claimed method relies on techniques well known to the art in order to assay statistical association of any given polymorphism with an atopy predisposition.

The unpredictability of the art, the state of the prior art, and the level of skill in the art

The Office Action states that there is a high level of unpredictability in associating any particular polymorphism with a phenotype. The Applicants disagree with this statement. The level of unpredictability is demonstrated by the prior art, the post filing art, and the instant specification.

Numerous post filing art describe predictably associating polymorphisms in TIM-1 gene with predisposition with an atopic disorder. Graves et al. in J Allergy Clin Immunol. 2005 Sep; 116(3):650-6 report a 15-bp insertion/deletion in exon4 of TIM1 being significantly related to atopy. Gao et al in J Allergy Clin Immunol. 2005 May; 115(5):982-8 present data correlating genetic variation in TIM-1 gene with asthma in African American population. Chae et al in Hum Immunol. 2003 Dec;64(12):1177-82 show that molecular variations in the promoter and coding regions of human TIM-1 gene are associated with susceptibility to asthma in Korean population. Hence, as described in the specification, polymorphisms in TIM-1 gene are predictably correlated to predisposition to develop atopy.

The Examiner presents a GeneCard analysis indicating 135 SNPs in the TIM-1 gene, asserting that the specification does not teach any association of these 135 polymorphisms with any type of atopy.

As discussed above, techniques for generating probes with specificity for any of the TIM-1 SNPs are routine in the art, and such probes are generated by straightforward techniques as a consequence of applying the claimed method. As discussed above association of polymorphisms in TIM-1 gene and predisposition to atopy has been described in the specification and numerous publications.

The Examiner refers to Kroese et al. (Genetics in Medicine, vol 6 (2004), p. 475-480) as post filing art which assertedly teaches that since disease conditions can be multigenic and etiologies population-dependent, that genetic tests should be evaluated in terms of their detection of:

- 1) a particular genetic variant;
- 2) for a particular disease;

- 3) in a particular population; and
- 4) for a particular purpose (Kroese et al., page 477).

Applicants respectfully submit that the presently claimed method fulfills each of these conditions.

- 1) The method as claimed teaches the detection of polymorphic sequences at a particular, well-defined genetic locus using probes for specific sequences;
- 2) atopic disorders are well-defined and routinely clinically reported;
- 3) the populations studied by the claimed method are clinically definable by the presence of disease; and
- 4) the specific purpose of the method as claimed, screening for a predisposition to atopy, plays to the strengths of genetic analysis precisely because the goal is association of an allele with a likelihood of disease. While discovery of the mechanistic etiology of the disease is desirable, and likely in the case of TIM-1, it is not prerequisite for the effectiveness of the method as claimed.

The Examiner states that Kroese et al. further suggest that all measures of test performance be presented with their 95% confidence intervals. Applicants submit that the major finding of the exemplified reduction to practice, the association of protection from atopy with the 157insMTTVP allele in the presence of HAV seropositivity, is presented with P values representing >95% confidence. HAV+ individuals with 1 or 2, 2, or a single 157insMTTVP allele are protected from atopy at P=0.0005, P=0.002, and P=0.004, respectively (Table 1). The critical findings of the analyses presented in Tables S2 through S4 likewise meet this standard. As such, the recommendations of Kroese et al. are satisfied by the present Example.

The Examiner refers to Lucentini (The Scientist, 2004, Vol 18, page 20) as post-filing art which states that it is common for follow-up studies to find gene-disease associations wrong. Applicants note that the Lucentini in the second column, first full paragraph presents recommendations for avoiding this error:

- 1) accounting for “prior probability”, a subjective but reasonable measure of how plausible the gene-disease association in question looked prior to the study; and
- 2) large enough sample size to avoid a cofounder population stratification effect.

Applicants respectfully submit that the presently claimed method fulfills both of these conditions:

1) As reviewed above, the importance of the TIM-1 gene family is described in the specification, which includes numerous referenced publications linking the TIM genes to multiple immune-mediated diseases and description of the important role of the receptor encoded by the TIM-1 gene in immunological responses. The specification further states in the introduction to Example 6, page 53, paragraph 193:

TIM-1 is expressed by activated CD4 T cells during the development of helper T cell (Th2) responses and appears to regulate cytokine production. Therefore, we postulated that HAV interaction with TIM-1 on lymphocytes could modify T cells in a manner that protects against atopy, and that polymorphisms in TIM-1 might alter susceptibility to atopy.

The introduction further states:

By sequencing lymphocyte cDNA, we identified a six amino acid insertion, 157insMTTVP. 157insMTTVP is located at the center of an extracellular mucin-like region that is required for efficient HAV uncoating, and because 157insMTTVP lengthens this critical region by 12-14%, this variation may impact the efficiency of viral entry.

As such, the prior probability of gene-disease association was reasonably considered to be high in the course of designing the experiment.

2) The population stratification effect results from the tendency of populations to carry high frequencies of both certain genes and certain diseases owing to common ancestry. As reviewed above, the purpose of the method as claimed is screening for a predisposition to atopy, not discovery of a causal link of polymorphism to disease. While discovery of the mechanistic etiology of the disease is desirable, and likely in the case of TIM-1, it is not prerequisite for the effectiveness of the method as claimed; genetic linkage alone is sufficient. Moreover, since the population displaying atopic conditions is large and diverse as evidenced in the present specification, the likelihood of founder effects is small, and the likelihood of such effects reducing the informativity of the data in a study comprising multiple ethnic groups is smaller.

Accordingly, the recommendations of Lucentini are satisfied with respect to the instant Application, substantiating the reliability of the exemplified results.

The Examiner refers to Noguchi et al. (Genes and Immunity (2003) 4: 170-173) as teaching a lack of association between polymorphisms in the TIM-1 gene and asthma in Japanese asthmatic families.

Applicants firstly note that none of the polymorphisms identified by Noguchi et al. were associated with asthma in the present experimental examples (specification, Example 6; Noguchi et al., page 170, right column, second full paragraph).

Applicants secondly note that the instant Example 6 was practiced upon individuals answering to calls for allergic reactions and responding positively for allergic rhinitis, atopic dermatitis and food allergy, and positive for specific IgE against local allergens, not for familial asthma (specification, page 57, paragraph 201). As such, there is no apparent contradiction between the results of Noguchi et al. and those of the present example.

Moreover, Applicants emphasize that it is nowhere recited or implied in the instant Application that every polymorphism of TIM-1 must carry predictive association with an atopic disease. The claimed method relies on techniques well known to the art in order to assess statistical association of any given polymorphism with an atopy predisposition.

The Examiner refers to Applicants' own post-filing art, Umetsu et al. (Ann NY Acad Sci, 2004, 1029:88-93), as teaching results which are confirmatory of those presented in the instant Application, namely, that serotype HAV+ insertion allele carriers are protected against atopy while HAV- carriers are not. As such, there is no apparent contradiction between the result of Umetsu et al. and those of the present examples.

Applicants emphasize that it is nowhere recited or implied in the instant Application that every polymorphism of TIM-1 will carry association with an atopic disease in the absence of any other infectious agent or associated gene. Applicants submit that there is no *a priori* reason that viral infection should be excluded from the characteristics of an individual suffering from atopy in whom the method finds use.

The Examiner refers to Graves et al. (J Allerg Clin Immunol 2005, vol 1 18, pages 650-656) as post-filing art reporting a study in which TIM family polymorphisms were assessed for multiple atopic condition in children of multiple ethnicities, finding that some alleles of TIM-1 displayed statistically significant association with atopy and some did not. One deletion polymorphism in exon 4 was found to be associated with atopy, multiple point mutants were not (Graves et al., i.e. abstract).

Applicants firstly note that none of the polymorphisms identified as not significantly associated with atopy by Graves et al. were found to be associated with atopy in the present experimental examples (specification, Example 6; Graves et al., page 170, right column, second full paragraph).

Moreover, Applicants emphasize that it is nowhere recited or implied in the instant Application that every polymorphism of TIM-1 must carry predictive association with an atopic disease. The claimed method relies on techniques well known to the art in order to assess statistical association of any given polymorphism with an atopy predisposition.

As such, there is no apparent contradiction, and indeed, given the differing polymorphisms assessed, there is significant consonance between the results of Graves et al. and those of the present example. Graves et al. find that multiple alleles show statistically significant association with atopic conditions (Graves et al., page 652, right column, second full paragraph). Graves et al. teach that these "associations were strong enough to remain significant after adjustment for multiple comparisons" (transition paragraph from page 653-654). Contra the Examiner, Graves et al. teach that although a limitation of the analysis is reflected in the ethnic heterogeneity of the Tucson population, similar results were replicated in children with two Caucasian parents, indicating that the significant associations are unlikely to be related to population stratification as the result of ethnicity (page 655, right column, third full paragraph). Accordingly, the study does not cast doubt upon but rather substantiates the rationale and feasibility of the claimed method.

Gao et al. report that genetic variants of the TIM-1 gene contribute to asthma susceptibility in the African-American population. In Gao et al., frequencies of the TT genotype for a single nucleotide polymorphism rs2277025 and a homozygous deletion variant 157delMTTVP in the fourth exon of the TIM-1 gene were higher among patients with patients with asthma compared with controls (odds ratio [OR], 2.779, P = .016; and OR, 3.09, P = .022, respectively). The association was further substantiated by haplotype analysis of these and two additional SNPs (OR, 2.48; P = .004), and also by family-based tests for the allele and haplotype carrying 157delMTTVP (P = .009 and P = .048, respectively). Accordingly, TIM-1 allelic variation has been statistically associated with atopic conditions in an African American population.

One of skill in the art is well-prepared by the instant specification to practice the claimed method. The relevant ordinarily skilled artisan is generally a skilled laboratory technician with experience in molecular biology and/or a scientist with the equivalent of a doctoral degree in molecular biology techniques. Furthermore, such artisans are required to keep abreast of the latest technology through continuing education and reading of scientific journal articles. As such, the skill level of those developing and using methods for manipulating DNA and performing nucleic acid-based assays is high. It would therefore be straightforward for one of

skill in the relevant art to distinguish TIM-1 alleles which are of use in the presently claimed method.

Quantity of experimentation

The courts have clearly taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. For example, see MPEP §2164.01.⁴

As the court explained⁵:

"[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed."

Practitioners in the chemical and molecular biological arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result. The Federal Circuit has found that such extensive experimentation is not undue in the molecular biology arts. For example, the court concluded that extensive screening experiments, while being voluminous, were not undue in view of the art which routinely performs such long experiments.⁶

The claims recite a method of screening for a human individual's predisposition to an atopy, the method including analyzing the individual for the presence of at least one TIM-1 polymorphism by contacting a biological sample including genomic DNA, mRNA or transcript thereof from an individual with probes that specifically bind under stringent conditions to the nucleic acid sequence of a TIM-1 allele, where the presence of the polymorphism is indicative of an individual's predisposition to develop an atopy.

The only experiments that need be performed to enable the entire scope of the claim are those designed to assess the association of a TIM-1 polymorphism with an atopic condition in a population of interest. The sequence of such a polymorphism is determined through routine experimentation, typically employing nothing more than performing the same assay disclosed in the specification on a clinically defined cohort using polypeptides made by routine, high-

⁴ See also *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd sub nom., *Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985).

⁵ *In re Wands* 8 USPQ 2d at 1404

⁶ *Hybritech v. Monoclonal Antibodies, Inc.* 231 USPQ 81 (Fed. Cir. 1986)

throughput sequencing and DNA synthesis techniques. Since these experiments are routine in nature, no undue experimentation is required. In other words, the only experimentation required to enable the claimed invention are experiments to confirm a statistical association of an allele in a population, and since this only requires a routine assay to determine, no undue experimentation is necessary.

In sum, the amount of experimentation required to establish conditions in which detection of a polymorphism in the TIM-1 gene permits the screening for a predisposition to atopy would not be undue because a) a working example has been provided, b) guidance on how to assess the association has been provided, c) it is straightforward to establish a reasonable correlation between atopy and members of the species within a genus of this breadth, and d) one of skill in the art would be able to perform such screening experiments as a matter of routine.

The specification therefore provides sufficient enablement such that one of ordinary skill in the art would be able to practice the invention without undue experimentation. Accordingly, Applicants respectfully request withdrawal of the rejection.

Claim Rejections- 35 U.S.C. 112- Written Description

Claims 1, 4, 7-8 and 20-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Office Action states that claims are broadly drawn to methods for diagnosing predisposition to any atopic immunological disorder comprising determining any polymorphism in any human individual (claim 1). It is asserted that the claims are broadly drawn to methods comprising the detection of a variety of nucleic acids, including any polymorphic variant of TIM-1 gene that is associated with any type of atopy. The Applicants respectfully disagree with the examiner.

Without any intention to acquiesce to the correctness of this rejection and solely to expedite prosecution, claims 1, 4, 8, 20 and 23 are amended.

A method of “diagnosing” has been amended to a method of “screening” for a human individual’s predisposition to atopy.

The term “nucleic acids” has been replaced by “DNA or mRNA”.

Claim 8 has been amended into an independent claim stating a method of screening for an individual’s predisposition to atopy, by analyzing the individual’s biological sample for the presence of an INS157 in TIM-1 gene by using a probe that specifically binds to the INS157

polymorphism, and analyzing the individual for HAV seropositivity, where the presence of HAV seropositivity and the INS157 polymorphism is indicative of a reduced risk of atopy.

Claim 20 has been amended to state a method of screening a human individual's predisposition to atopy by analyzing the individual's biological sample for the presence of INS157 in TIM-1 gene by using a probe that specifically binds to the INS157 polymorphism, where the presence of the INS157 polymorphism is indicative of the individual's predisposition to develop atopy.

Claim 23 has been amended to state a method of screening for a human individual's predisposition to atopy by analyzing the individual for the presence of polymorphisms in exon 3 with probes that specifically bind under stringent conditions to a polymorphism in exon 3 of a TIM-1 gene.

The applicants respectfully submit that the claims are drawn to methods of screening individual's for disposition to atopy. Atopy is a well characterized with underlying immune dysfunction which manifests in specific clinical phenomenon. The art refers to this condition in multiple references provided herein.

The Applicants respectfully submit that in contrast to the Examiner's statement of the claims being broadly drawn to detection of any polymorphism, the claims are drawn to detecting polymorphisms specific to TIM-1. Claims 4, 8, 20-22 further limit claim 1 to detection of an INS157 polymorphism in TIM-1. Claim 23 is limited to detection of polymorphisms in exon 3 of TIM-1.

On the contrary to the Examiner's statement that the claims are broadly drawn to methods comprising detection of a variety of nucleic acids, the claims are drawn to detection of nucleic acid sequences found in TIM-1. To clarify this point, the Applicants have amended the claims to state that a detection of DNA or mRNA is used.

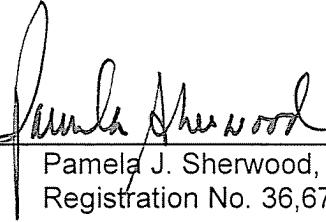
The Applicants submit that this aspect of the rejection has been addressed. In light of the amendments withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-235CIP.

Respectfully submitted,
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